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400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,000	ENDO ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) *12-16,18, 19 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,20-24 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9, 12-16 and 18-28 are all the pending claims for this application.

2. Applicant's amendment to the specification of 1/18/05 to cross-reference the application to the PCT priority document has been considered and entered.

Election/Restrictions

3. Applicant's election with traverse of Group I (Claims 1-9, 20, 24 and 28) in the reply filed on 3/29/07 is acknowledged. The traversal is on the ground(s) that unity of invention for the claims was found for the corresponding PCT application during international examination and there is no serious search burden. This is not found persuasive because 37 CFR 1.499 (MPEP 1893.03(d)) provides that an examiner *may* require the restriction of claims for a national stage application that lacks unity of invention under §1.1475. Additionally, Applicant has not provided any technical arguments why the lack of unity restriction is improper or why the inventive groups are coextensive for searching purposes. Finally, Applicants are also reminded that an Examiner is not required to establish a search burden in finding lack of unity much less where a lack of unity restriction is required for a 371 application. Chapter 1800 of the MPEP does not speak to this issue.

The requirement is still deemed proper and is therefore made FINAL. However, because the immobilized scFv of Claims 24 and 28 depend from Claim 21 as being drawn to a method for making an immobilized scFv, Claims 21-23 have been rejoined.

4. Claims 12-16, 18, 19, and 25-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (Group II), there being no allowable generic or linking claim.

5. Claims 1-9, 20-24 and 28 are all the pending claims under examination.

Information Disclosure Statement

6. The U.S. and international patent references and the non-patent literature references cited in the IDS of 1/18/05 have been considered and entered.

Specification

The disclosure is objected to because of the following informalities:

7. Pursuant to 37 CFR 1.821(c), a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The description for figure 1 (p. 14, lines 25-26) does not recite sequence identifiers for the two peptide sequences disclosed in Figure 1

8. The use of the trademark, Minisart™, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are advised to carefully check the entire specification for any other improperly identified trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-9, 20-24 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-9, 20-24 and 28 are indefinite for the recitation that the antibody "carries" or is "carrying" a labeling substance in the linker part in Claims 1 and 21 because it is not clear what the structural relationship is between the labeling substance and the linker part of the antibody. Are the two molecules chemically attached? What sort of association or biochemical interaction is meant by the term "carrying"? Is this a dissociable reaction or a conjugate?

b) Claims 9 and 28 are indefinite for the recitation the antibody "has a Kd value that is equivalent to a Kd value of a naturally occurring antibody" because it is not clear what reference antibody is being compared to. Is the naturally occurring antibody the parental or wild-type antibody of the single chain antibody?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Luo et al. (J. Biotechnol. 65:225-228 (1998); cited in the IDS of 1/18/05 and the PTO 892 form of 3/12/07).

Claims 1 and 2 are drawn to a single chain antibody comprising a linker where the linker comprises a labeling substance. The antibody is not limited as to where the linker part should occur within the structure of the single chain antibody or how the linker relates structurally or functionally to the labeling substance.

Luo discloses a scFv with a C-terminal extension comprising a biotin mimetic sequence (BMS) or c-Myc-BMS for use as an in vitro diagnostic. The BMS is disclosed as have high affinity for streptavidin (p. 226, Col. 2, ¶3).

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (Cancer Res. 60:6663-6669 (2000)).

The interpretation of Claims 1 and 2 is discussed supra.

Schultz discloses a scFvSA construct where the scFv comprises Vh and Vl domains from the anti-CD20 antibody fused to the full length streptavidin and linker sequences are interposed between the Vh and Vl domains, and between the Vl and SA domains as shown in Figure 2. Schultz discloses the SA domain as a label for binding to biotin.

12. Claims 1-8 are rejected under 35 U.S.C. 102 (b) as being anticipated by Mascarenhas et al. (USPN 5914254; published June 22, 1999).

The interpretation of Claims 1 and 2 is discussed supra. Claims 3-8 are drawn to the antibody of heavy and light chains or variable regions carrying a labeling substance in the linker and the labeling substance binds to a polypeptide of the linker in the presence of an enzyme (Claims 3 and 4) or where the labeling substance is incorporated into the linker (Claims 5 and 6) or where the labeling substance is biotin and the enzyme is biotin ligase (Claims 7 and 8).

Mascarenhas discloses fusion proteins comprising single chain antibodies having linker peptides inserted between the two domains of interest (e.g., the VH and VL domain), where linker peptides can serve as an "affinity tag" to aid in the purification of the fusion polypeptide away from other cellular polypeptides, for example, multiple

histidine residues, or where the linker peptide comprises a biotinylation sequence which is recognized by biotin holoenzyme synthetase.

13. Claims 1-9, 20-24 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002).

The interpretation of Claims 1-8 is discussed supra. Claim 9 is drawn to the antibody of heavy and light chains or variable regions carrying a labeling substance in the linker, where the antibody has a Kd similar to a naturally occurring antibody produced by wheat embryo cell-free translation system (Claim 9). Claims 20-23 are drawn to methods for immobilizing the single chain antibodies of the invention by reaction with a binding substance recognized by the labeling substance. Claims 24 and 28 are drawn to immobilized single chain antibodies and having a Kd similar to a naturally occurring antibody produced by wheat embryo cell-free translation system.

Fricker discloses a probe comprising an "idiotype network" comprising i) a target binding site moiety (e.g., idiotype scFv) which is attached to a first fluorescent polypeptide; (ii) a mimic moiety (e.g., anti-idiotype scFv) which is capable of binding to the target binding site moiety and which is attached to a second fluorescent polypeptide; and (iii) a linker which connects the two fluorescent polypeptides, where the linker comprises one or more of: (1) a sequence capable of being recognised and bound by an immobilized component; (2) a protease cleavage site; (3) a non-analyte binding site; (4) two or more copies of the sequence (SerGly.sub.3); or (5) one or more copies of a

rod domain from a structural protein [0122]. Fricker discloses probes comprising a biotinylation peptide sequence, where for example the mimic moiety comprises such a sequence [0057] and biotinylated probes are produced by a 17 residue biotin acceptor sequence that acts as a substrate for biotin ligase and permits the creation of endogenously biotinylated proteins [0059]. Fricker discloses a peptide sequence capable of being recognised and bound by an immobilised component such as a hexa-histidine tag (His_6), an antibody epitope, or a sequence recognised by a protein modification enzyme (for example a biotinylation site, glycosylation site or a phosphorylation site) [0081]. Fricker discloses producing the probes in cell-free translation systems [0055] including wheat [0158].

The claims are not limited to the heavy and light chain domains for the single-chain antibody being directly cross-linked through the linker, therefore the probe for an "idiotype network" disclosed in Fricker reads on, and therefore anticipates the instant claims. The claims are not limited to exclude other components as part of the single chain antibody such as first and second fluorescent proteins, therefore, the "idiotypic network" of Fricker reads on, and therefore anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-9, 20-24 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas et al. (USPN 5914254; published June 22, 1999) in view of Fricker et al. (US20040265902; published December 30, 2004; filed May 10, 2002).

The interpretation of Claims 1-9, 20-24 and 28 is discussed supra.

The claimed single chain antibodies were prima facie obvious at the time of the invention over Mascarenhas in view of Fricker.

The interpretation of Mascarenhas is discussed supra. Mascarenhas does not teach expression of the single chain antibodies in cell-free systems such as wheat or method for making immobilized antibodies or immunobilized antibodies. Fricker recitifies this deficiency in its disclosure.

The interpretation of Fricker is discussed supra.

One skilled in the art would have been motivated to have produced the instant claimed antibodies, method for producing an immobilized antibody and immobilized antibody based on the combined disclosures of Mascarenhas and Fricker. Both Mascarenhas and Fricker explicitly teach single chain antibodies which are fusion proteins (or are a part of a fusion protein such as Fricker) having peptide linkers or spacers which further comprise or have inserted within the spacer/linker a labeling molecule such as polyhistidine tag or biotinylation peptide sequence. Each of the references recognizes the biotin/biotin ligase reaction for producing a biotin label for further interaction with a streptavidin substrate, and Ficker extends this to methods for immobilization of the antibody (the "idiotype network") to produce immobilized antibodies. Fricker discloses cell-free translation of the antibodies and expression in wheat. Because Fricker discloses producing a multimeric scFv complex under these conditions, one skilled in the art could have readily modified the scFv of Mascarenhas to include His tag labels inserted within the peptide linker within the linker in order to arrive at the instant claimed single chain antibodies, immobilization methods and immobilized forms thereof. One could have reasonably expected to have achieved the single chain antibodies and methods of the instant claims because the reagents were available and the techniques for producing single chain antibodies much less the fusion proteins such as the "idiotype network" of Fricker were within ordinary skill of the art at the time of the invention. Each of the references also appreciates the convenience of an internal or linker-associated label which facilities purification or identification of the single chain

antibody or which can be used to easily immobilize the antibody by binding of the label to its recognition site. Further because the scFv of Mascarenhas is a simplification of the "idiotype network" of Fricker (or seemingly structurally less complex), one would have been further motivated to have combined the references and been assured of success in doing so to produced immobilized forms of the antibodies and expressed in wheat embryo translation systems. For all of these reasons, the claims were prima facie obvious at the time of the invention over Mascarenhas and Fricker.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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